

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000078

International filing date: 21 January 2005 (21.01.2005)

Document type: Certified copy of priority document

Document details: Country/Office: IL
Number: 161012
Filing date: 22 March 2004 (22.03.2004)

Date of receipt at the International Bureau: 01 March 2005 (01.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

114,6

PCT/IL 05 / 000078



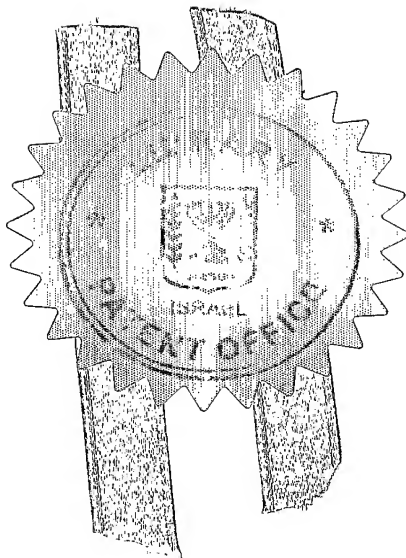
מדינת ישראל
STATE OF ISRAEL

Ministry of Justice
Patent Office

משרד המשפטים
לשכת הפטנטים

This is to certify that
annexed hereto is a true
copy of the documents as
originally deposited with
the patent application
particulars of which are
specified on the first page
of the annex.

זאת לתעודה כי
רצופים בזה העתקים
נכונים של המסמכים
שהופקדו לכתחילה
עם הבקשה לפטנט
לפי הפרטים הרשומים
בעמוד הראשון של
הנספח.



This 01-02-2005 היום
ממונה על/חברות
רשם הפטנטים
Commissioner of Patents

נתאשר
Certified

לשימוש הלישכה
For Office Use

161012

מספר:
Number

תאריך:
Date

22-03-2004

הוקדם/נדחה
Ante/Post-Dated

חוק הפטנטים, תשכ"ז-1967
Patent Law, 5727 - 1967
בקשה לפטנט
Application for Patent

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)

I, (Name and address of applicant, and in case of body corporate-place of incorporation)

M.D.Z. INVESTMENTS LTD
78 Hadasa St.
Beer-Sheva 84221

מ.ד.צ. השקעות בע"מ
רח' הדסה 78
באר-שבע 84221

Owner, by virtue of The Law
of an invention the title of which is

הדין בעל ההמצאה מכח
ששמה הוא

שיטת טיפול בסטומטיטיס אפתי בפה ובמוקוסיטיס בפה

(בעברית)
(Hebrew)

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL
MUCOSITIS

(באנגלית)
(English)

hereby apply for a patent to be granted to me in respect thereof. מבקש בזאת כי ינתן לי עליה פטנט.

*בקשת חלוקה - Application of Division	*בקשת פטנט מוסף - Application for Patent Addition	*דרישה דין קדימה Priority Claim		
*מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
מס' _____ dated _____ מיום	מס' _____ dated _____ מיום			
*יפוי כח: כללי / מיוחד - רצוף בזה- / ע"ד יוגש P.O.A.: general /-individual- attached /-to be filed later הוגש בעניין _____ 160022 _____				
המען למסירת מסמכים בישראל Address for Service in Israel לוצאטו את לוצאטו ת.ד. 5352 מספרנו: 17298/04 באר שבע 84152				
חתימת המבקש Signature of Applicant		היום 21 בחודש מרץ שנה 2004 of the year of This		
Luzzatto & Luzzatto By: Attorneys for Applicant		לשימוש הלישכה		

טופס זה כשהוא מוטבע בחותם לישיכת הפטנטים ומושלם במספר ובתאריך ההגשה, הינו אישור להגשת הבקשה שפרטיה רשומים לעיל.
This form, impressed with the Seal of the Patent Office and indicating the number and date of filing, certifies the filing of the application the particulars of which are set out above.

*מחק את המיותר Delete whatever is inapplicable

17298/04

שיטת טיפול בסטומטיטיס אפתי בפה ובמוקוסיטיס בפה

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL MUCOSITIS

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL MUCOSITIS

Field of the Invention

5 The present invention relates to a two-component composition for ameliorating, treating, and preventing oral mucosa disorders, including aphthous stomatitis, wherein said components, namely a quinoline derivative and an antiseptic, are applied either simultaneously or subsequently.

10

Background of the Invention

Canker sores, or aphthae, are the most common oral disease which affects, in some degree, up to two thirds of the population, causing discomfort and annoyance to millions of people around the globe. The disease has unclear
15 etiology, and it is also denoted, in various of its symptoms, as recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), or ulcerative stomatitis. RAU are characterized by repeated development of painful sores. The small, shallow and rounded ulcers develop inside the mouth, especially on the mucosa of the cheeks, lips, floor of mouth, lateral and
20 ventral sites of the tongue, and only on rare occasions on the gums or the palate. The lesions caused by RAU may reappear at intervals of a few months to a few days. The most common presentation of the disease is

minor aphthae (MiRAU) affecting about 80% of RAU patients, which is characterized by recurrent, round, clearly defined, small, painful ulcers, usually less than 5 mm in diameter with a gray-white necrotic pseudomembrane cover and a thin erythematous halo. MiRAU occur
5 usually on the non-keratinized oral mucosa, i.e., labial and buccal mucosa as well as vestibulum and floor of mouth. These lesions may heal within 10 to 14 days without scarring. Major aphthae (MaRAU) are a less common form of the disease and are usually characterized by recurrent large ulcerations, which may be 1 to 3 cm in diameter. MaRAU occurs
10 mainly on labial, buccal, latero-ventral mucosa of the tongue and may persist up to 6 weeks and often heal with scarring. The third and the least common clinical form of RAU are the herpetiform aphthae (HA) that is characterized by multiple (up to 100) recurrent clusters of pinpoint (2 - 3 mm diameter) painful ulcers, which tend to fuse, producing large areas of
15 erosions and ulcerations. This resembles the clinical presentation of primary herpetic gingivo-stomatitis – a viral disease caused by human herpes virus type I. HA may occur on the entire oral mucosa, including keratinized mucosa, such as that of the gingiva and palate. It has a later age of onset than MiRAU and MaRAU.

20

From 5% to 66% of the population, depending on the group studied, are afflicted. Studies found that RAU have a tendency to recur along family lines, and a high correlation of RAU has been detected in identical twins

[Miller M.F. et al.: Oral Surg. Oral Med. Oral Pathol. 43 (1977) 886-91].

Women seem to be afflicted slightly more than men. The disease seems to be less frequent, e.g., among Bedouin Arabs, but is very common in North America. Although the etiology of RAU is unknown, numerous systemic

5. and local factors have been proposed to be involved in its pathogenesis.

Among the local factors, minor trauma, such as anesthetic injections, sharp foods or trauma from dental treatment, should be considered as one of the precipitating factors of RAU. It has been suggested that oral *Streptococci* and several viruses may play an etiologic role in RAU;

10. however, no conclusive results have been achieved. The involvement of inflammatory cytokines in RAU was implicated [Buno I.J. et al.: Arch.

Dermatol. 134 (1998) 827-31]. RAU was also associated with immune disturbances [Eversole L.R. Oral Surg. Oral Med. Oral Pathol. 77 (1994)

555-71]. The systemic and local cellular immunodisregulation associated

15. with RAU seems to be consistent with a viral reactivation, and may be a

result of a latent viral infection of oral mucosa [Pedersen A. et al.: Oral

Pathol. Med. 22 (1993) 64-8]. RAU was also observed in several systemic

disorders, such as Behcet's disease, cyclic neutropenia, MAGIC syndrome,

FAPA syndrome, celiac disease, inflammatory bowel disease, HIV, ulcer

20. vulvae acutum, and hemato-deficiencies, such as iron, zinc, and vitamin

deficiencies [Ship J.: Oral Surg. Oral Med. Oral Pathol. Oral Radiol.

Endod. 81 (1996) 141-7]. There is no specific treatment for RAU, and the

management usually depends on the symptoms, duration and severity of

the ulcerative lesions. In cases of RAU resulting from a systemic disorder, the corresponding therapy for said disorder can be efficient, for example in cases of a nutritional or vitamin deficiency, a replacement therapy is used.

5 Despite detailed clinical and research investigation over the years, the causes of the disease, first described by Hippocrates, are still unknown, and no effective management is available for it. Therefore, a need is felt for new means that could either heal aphthae or at least ameliorate them more efficiently.

10

The disorders of mouth mucosa, being manifested by vesicular-bullous ulcerative, or erosive, lesions, may be diagnosed also as chronic discoid lupus erythematosus, herpetiform dermatitis, pemphigus family disorders, pemphigoid family disorders, linear IgA disorders or other
15 immunoregulatory disorders, and similarly to the aphtae family, their exact etiology is unclear; they are quite common – but less frequent than aphtae. To this greater family of mouth mucosa disorders, radiotherapeutic mucositis and chemotherapeutic mucositis, the conditions caused by radiotherapy and chemotherapy, may be added, even
20 though in this case, etiology is clearer, and involves cytotoxic effects of said therapies. What is common to all the mentioned oral mucosa disorders, including aphthae related disorders, is the lack of knowledge regarding the precise mechanism by which they develop, and the lack of

efficient therapies for these painful conditions. All said mouth mucosa disorders will be called oral mucositis hereinafter.

The most common treatment for oral mucositis of various origin is topical
5 therapy, which may include antimicrobial and analgesic mouthwashes,
topical or systemic glucocorticoids, immunosuppressors and hormones.
The most common topical therapy is the use of hydrocortisone,
triamcinolone, fluocinonide, betamethasone and flumethasone [Scully C.
et al.: J. Oral Pathol. Med. 18 (1989) 21-7]. Immunosuppressive drugs,
10 such as colchicine, cyclosporin and thalidomide, as well as
immunopotentiating agents, such as levamisole, gammaglobulin and
longovital were also tried without clear results. Some topical medications
seemed to have certain beneficial effects on the ulcers of RAU, such as
sucralfate [Ratan J. et al.: J. Int. Med. 236 (1994) 341-3], azelastine
15 hydrochloride [Ueta E. et al.: J. Oral Pathol. Med. 23 (1994) 123-9],
prostaglandin E2 [Taylor L.J. et al.: Br. Dent. J. 175 (1993) 125-9],
listerine [Meiller T.F. et al.: Oral Surg. Oral Med. Oral Pathol. 72 (1991)
425-9], diclofenac in hyaluronan [Saxen M.A. et al.: Oral Surg. Oral Med.
Oral Pathol. Oral Radiol. Endod. 84 (1997) 356-61], or bioadhesive
20 hydrogel patches [Mahdi A.B. et al.: J. Oral Pathol. Med. 25 (1996) 416-9].
All said treatments are palliative, reducing the symptom manifestation.
US 5,686,095 discloses a method for topically treating aphthous
ulcerations, comprising fluoroquinolone derivatives.

Copending IL 160022 of the same inventors provides a composition for treating aphthous stomatitis and oral mucositis, comprising quinoline derivatives. It is an object of this invention to provide a still more efficacious pharmaceutical composition for treating aphthous stomatitis
5 and oral mucositis, particularly when secondary complications occur.

It is further an object of this invention to provide an efficacious pharmaceutical composition for accelerated healing of aphthae, and for mitigating pains caused by them, even when these conditions are
10 accompanied by secondary infections. It is a still further object of the invention to provide an efficacious composition for aphthae prevention.

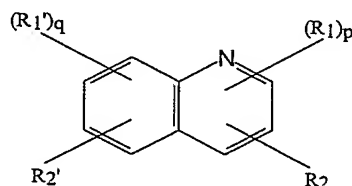
Other objects and advantages of present invention will appear as description proceeds.

15

Summary of the Invention

The present invention provides a two-component pharmaceutical composition for ameliorating, treating, and preventing oral mucosa disorders, including canker sores associated with aphtha minor, aphtha
20 major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous ulcerative or erosive lesions, pemphigus family disorders, pemphigoid family disorders, linear

IgA disorders or other immunoregulatory disorders, herpetiform dermatitis, chronic discoid lupus erythematosus, radiotherapeutic mucositis, and chemotherapeutic mucositis, wherein said disorders may be complicated by secondary infections, wherein said two components may be applied simultaneously or subsequently, said two components being an antiseptic and a quinoline derivative of formula I:



I

or its stereoisomer, or its pharmaceutically acceptable salt, wherein R_1 and R_1' are independently selected from -H, -Cl, -F, C_1 - C_3 alkyl, C_1 - C_3 alkyloxy, and $-CF_3$; R_2 and R_2' are independently selected from -H, -NH(R_3), and -C(OH)(R_3), wherein R_3 is selected from phenyl and C_3 - C_6 alkyl, substituted with 1 to 3 substituents selected from C_1 - C_2 alkyl, ethenyl, -OH, and -NH₂, and wherein said -NH₂ is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl or the nitrogen atom of said -NH₂ is connected with 1 or 2 carbon atoms of said C_3 - C_6 alkyl or C_1 - C_2 alkyl, possibly forming bicyclic structure; p is an integer from 1 to 3, and q is an integer from 1 to 4. Said antiseptic is selected from acceptable antiseptics known in the art, such as chlorhexidine, thymol, esters of p-hydroxybenzoic acid, etc.

Any of the two components of said two-component composition may further comprise a component selected from solvents, buffers, carriers, binding agents, stabilizers, adjuvants, diluents, excipients, surfactants, and odorants, as well as another pharmaceutically active substance
5 selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, and antineoplastic. The composition of this invention is used topically.

This invention also relates to a method for treating, ameliorating, and
10 preventing conditions comprising the appearance on the oral mucosa of painful sores, vesicles, bullae, ulcers, erosions, lesions, or blisters, associated for example with aphthae, discoid lupus erythematosus, pemphigus, pemphigoid, herpetiform dermatitis, radiotherapy and chemotherapy, wherein said conditions may be accompanied by a
15 secondary infection, comprising the steps of i) providing a quinoline derivative of formula I as defined above, or its stereoisomer or a pharmaceutically acceptable salt thereof; ii) providing an antiseptic, iii) preparing two formulations comprising separately said antiseptic and said quinoline derivative or its isomer or salt, or preparing one formulation
20 comprising a mixture of said antiseptic and quinoline derivative in solution or suspension, wherein said formulations may further comprise components adjusting the consistency, stability, and olfactory properties, and optionally additional active substances; and iv) administering said

formulation(s) to a patient in need of the treatment, wherein said two components may be administered simultaneously or subsequently. Said administration of said formulation(s) comprises rinsing, spraying, and applying ointment or adhesive patch. In a preferred method according to this invention, a mucosa disorder associated with aphtha is treated by rinsing mouth several times a day with a liquid comprising said quinoline derivative, and several times a day with a liquid comprising an antiseptic, selected, e.g., from a esters of p-hydroxybenzoic acid, thymol, and chlorhexidine.

10

Detailed Description of the Invention

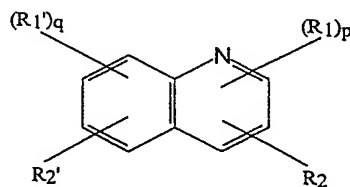
It has now been found that oral aphthous stomatitis and oral mucositis are efficiently healed when treated by both antiseptics and quinoline derivatives. For example, patients with major aphtha accompanied by a secondary infection achieved relief of pains and healing through rinsing their mouth with a two-component composition, the first component comprising quinine, and the second one chlorhexidine, the rinses with the two components being preferably performed consequently, each rinsing performed for several minutes, each double-rinse performed several times a day.

20

Aphthous stomatitis and oral mucositis is often accompanied by a secondary infection, which can aggravate the symptoms and complicate the treatment. The composition according to the invention is useful also for these complicated cases, offering a synergistic effect provided by the
5 two-component system.

Whenever the term "two-component composition" is used herein, a system is meant that comprises at least one antiseptic and at least one quinoline derivative of formula I, wherein the two components may be mixed,
10 forming a homogeneous formulation to be applied simultaneously, or alternatively the two components may be separated and applied subsequently in any order. It is understood that said term does not exclude the presence of other components.

15 In a preferred embodiment of this invention, a two-component composition comprising an antiseptic selected from accepted antiseptics, such as chlorhexidine or esters of p-hydroxybenzoic acid, and a quinoline derivative of formula I:



I

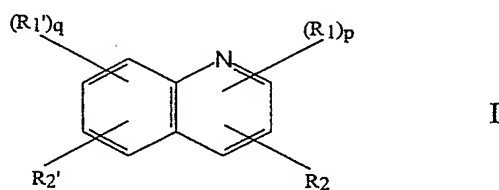
or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_1' are independently selected from -H, -Cl, -F, C_1 - C_3 alkyl, C_1 - C_3 alkyloxy, and $-CF_3$; R_2 and R_2' are independently selected from -H, -NH(R_3), and -C(OH)(R_3), wherein R_3 is selected from phenyl and C_3 - C_6 alkyl, substituted with 1 to 3 substituents selected from C_1 - C_2 alkyl, ethenyl, -OH, and -NH₂, and wherein said -NH₂ is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said -NH₂ is connected with 1 or 2 carbon atoms of said C_3 - C_6 alkyl or C_1 - C_2 alkyl, forming secondary or tertiary amine, possibly forming bicyclic structure; p is an integer from 1 to 3; and q is an integer from 1 to 4; is applied on oral mucosa afflicted with sores, ulcers, erosions, vesicular-bullous lesions, blisters, stria, or other painful changes, in form of a solution, suspension, gel, emulsion, ointment, patch, or spray; wherein both components are applied simultaneously or subsequently. When the components are applied separately, the number of treatments performed daily with said quinine derivative and with said antiseptic need not be the same (for example, three quinine mouth washes may be interspersed with two chlorhexidine washes, etc.). Said solution and suspension are preferably based on aqueous solutions of pharmaceutically acceptable salts and buffers, such as physiological solution, etc, but may contain acceptable non-aqueous solvents, such as ethanol, DMSO, etc. Said gel, emulsion, or ointment may comprise pharmaceutically acceptable

oils and surfactants, and are prepared by methods known in the art of topical formulations, therefore not requiring detailed descriptions for their preparations. Said active agent of formula I may be either dissolved in at least one phase of the composition, or may be partially dispersed. Said
5 ester of p-hydroxybenzoic acid may be selected from methyl, ethyl, propyl, and butyl.

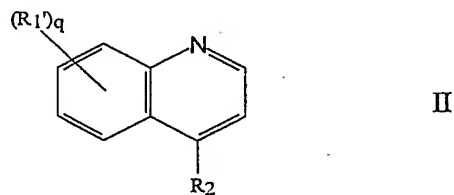
The composition of the invention is applied preferably on the oral mucosa afflicted with a disorder selected from canker sores associated with aphtha
10 minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous erosive or ulcerative lesions, pemphigus family disorders, pemphigoid family disorders (e.g. cicatricial), linear IgA disorders or other immunoregulatory disorders, herpetiform dermatitis, discoid lupus
15 erythematosus, radiotherapeutic mucositis, or chemotherapeutic mucositis. In a preferred embodiment of this invention, the two-component composition is applied on oral mucosa further afflicted by an accompanying infection.

20 In a preferred embodiment of the invention, the two-component composition for mitigating and healing symptoms of oral mucositis comprises an antiseptic and a quinoline derivative of formula I:



wherein R_1 and R_1' are independently selected from $-Cl$, $-OCH_3$, and $-CF_3$;
 one of R_2 and R_2' is $-H$ and the other is selected from $-NH(R_3)$, and
 5 $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_5 alkyl,
 substituted with 1 to 2 substituents selected from C_1-C_2 alkyl, ethenyl,
 and $-NH_2$, and wherein either said $-NH_2$ is optionally substituted with one
 or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom
 of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3-C_5 alkyl or
 10 C_1-C_2 alkyl, possibly forming bicyclic structure; and wherein the sum of p
 and q is an integer from 1 to 3; wherein said two components may be
 applied simultaneously or subsequently.

In a preferred embodiment of the invention, the two-component
 15 composition for ameliorating or treating or preventing oral mucositis
 comprises an antiseptic and a quinoline derivative of formula II:



wherein

R₁' is selected from -Cl, C₁-C₃ alkyloxy, and -CF₃; R₂ is selected from -NH(R₃), and -C(OH)(R₃), wherein R₃ is C₃-C₆ alkyl substituted with 1 to 3 substituents selected from C₁-C₂ alkyl, ethenyl, and -NH₂, and wherein said -NH₂ is either optionally substituted with one or two groups selected
5 from ethyl and hydroxyethyl or the nitrogen atom of said -NH₂ is connected with 1 or 2 carbon atoms of said C₃-C₆ alkyl or C₁-C₂ alkyl, possibly forming bicyclic structure, and wherein q is 1 or 2; wherein the two components may be applied simultaneously or subsequently.

10 In a preferred embodiment of this invention, oral mucositis is treated by a two-component composition comprising solutions or dispersions comprising hydroxychloroquine (HCQ) or its salt, and chlorhexidine. Preferably HCQ salt is dissolved in an aqueous buffered solution, and used several times a day for rinsing mouth (without swallowing), followed by
15 rinsing with chlorhexidine solution. The concentration of HCQ or its salt in said solution is preferably from 1 to 10 mg/ml, and the rinsing is preferably performed 3-5 times a day. HCQ is preferably used as sulfate. Chlorhexidine solution has preferably a concentration from 0.05% to 0.2 %.

20

In other preferred embodiment of this invention, oral mucositis is treated by a quinine (Q) salt in solution or suspension, which is used several times a day for rinsing mouth (without swallowing), followed by rinsing with

chlorhexidine solution. The concentration of Q is preferably from 1 to 10 mg/ml, and chlorhexidine solution has preferably a concentration from 0.05% to 0.2 %. The rinsing with each of the two components is preferably performed 3-5 times a day. Said Q solution may comprise Q dihydrochloride, Q hydrochloride, Q sulfate, and other Q salts. Said Q suspension may, for example, comprise Q sulfate. Stereoisomers of quinine and their salts, such as quinidine sulfate, have been also found active.

The invention provides a method for treating a symptom associated with oral mucositis selected from canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, bullous erosive or ulcerative lesions, pemphigus disorders, pemphigoid disorders, linear IgA disorders and other immunoregulatory disorders, chemotherapeutic mucositis, and radiotherapeutic mucositis, comprising preparing a two-component-composition, one component being an antiseptic and the other one a quinoline derivative of formula I or a pharmaceutically acceptable salt thereof, in form of paste, cream, gel, patch impregnated with an active agent, or spray, and applying said composition onto the painful areas or areas afflicted with the pathological changes, wherein the application of the two components may be simultaneous or subsequent. Other pharmaceutically effective agents may be present in the composition of the invention, to enhance the healing process, and taking into account

eventual other disorders involved. In one preferred embodiment, the method of the invention comprises an adhesive patch impregnated with a two-component composition containing an antiseptic and a quinoline derivative of formula I, which patch is placed on the inflicted areas repeatedly, until the pain and other aphthae symptoms disappear. In another preferred embodiment an adhesive patch may comprise only the quinoline component of the two-component composition, and the antiseptic component is applied through subsequent rinsing. In still another preferred embodiment, mouth rinsing with a liquid composition according to this invention is performed several times a day.

In a preferred use according to this invention, a composition comprising an antiseptic and a quinoline derivative, preferably selected from HCQ, quinine, their isomers and derivatives, and their salts, prolong the recurrence periods in persons suffering from RAU. Applying said two-component composition, either through simultaneous presence of both components or through their subsequent use, ameliorates the symptoms, heals ulcers, and typically also prevents the reappearance of new ulcers.

A composition according to the invention may comprise a component selected from solvents, buffers, carriers, binding agents, stabilizers, adjuvants, diluents, excipients, surfactants, flavors, and odorants. In a preferred embodiment of this invention, the composition for treating oral

aphthous stomatitis and oral mucositis, comprises another pharmaceutically active substance selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, and antineoplastic compounds. In a preferred embodiment said solvents comprise an aqueous solution. Non-aqueous solvents may be used in the composition of the invention, not only to adjust the required consistency of the composition or the solubility of the components, but also to synergistically improve the efficiency of the composition.

10 In a preferred embodiment of this invention, the composition is applied topically, by rinsing the afflicted area or washing the mouth, or alternatively spraying the afflicted area. The time of action of the healing composition of this invention is prolonged when an adhesive patch impregnated with said two-component composition, or with one of its components, is applied onto the afflicted area.

The invention will be further described and illustrated in the following examples.

20 Examples

Materials

Hydroxychloroquine (HCQ) was obtained from Sanofi-Syntelabo, Inc. N.Y.

USA, quinine (Q) and quinidine sulfate were obtained from Rakah, Holon, Israel. The compounds were used in concentrations 1-10 mg/ml, in tap water. Chlorhexidine was obtained from LACER S.A., Barcelona, Spain.

Example 1

5 A 50-year old woman, generally in good health, presented a most painful, distressing major aphtha of approximately 1 cm diameter on the ventro-lateral tongue. She had suffered the presence of such lesions for several years (recurrences of 6 to 8 episodes per year). The current lesion had been
10 present for about one week. During examination 2 lymph nodes were palpated in the floor of mouth, probably due to a secondary infection. She started to apply a rinse with 3.72 mg/cc HCQ solution (for 3 to 5 minutes) followed by a rinse with 0.12% chlorhexidine alcohol free solution (for about 1 minute), 3 times a day. Two days later, the patient was totally
15 free of pain and the size of the aphtha diminished to about 7 mm diameter. After 2 additional days of treatment, the aphtha completely disappeared.

Example 2

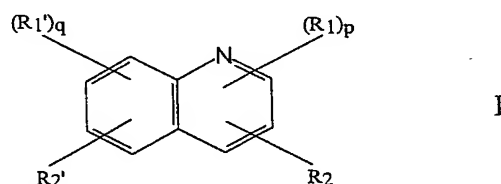
A 37-year old male, presented a painful minor aphtha on the ventro-
20 lateral part of the tongue. He reported its appearance about 1 week ago. In the past, frequent episodes of minor aphthae had occurred every 2 months. He started to rinse with 10 ml of quinine sulfate solution 3 mg/cc (for 3 to 5 minutes) followed by a rinse with 0.12% chlorhexidine alcohol free

solution (for about 1 minute), 3 times a day. The pain decreased significantly within 24 hours, and all the inconvenience disappeared within 48 hours.

- 5 While this invention has been described in terms of some specific examples, many modifications and variations are possible. It is therefore understood that within the scope of the appended claims, the invention may be realized otherwise than as specifically described.

CLAIMS

1. A two-component composition for ameliorating, treating, and preventing aphthous stomatitis and oral mucositis, comprising an antiseptic, and a quinoline derivative of formula I:



or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_1' are independently selected from -H, -Cl, -F, C_1 - C_3 alkyl,

C_1 - C_3 alkyloxy, and $-CF_3$;

R_2 and R_2' are independently selected from -H, $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3 - C_6 alkyl, substituted with 1 to 3 substituents selected from C_1 - C_2 alkyl, ethenyl, -OH, and $-NH_2$, and wherein said $-NH_2$ is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3 - C_6 alkyl or C_1 - C_2 alkyl, possibly forming bicyclic structure;

p is an integer from 1 to 3; and q is an integer from 1 to 4;

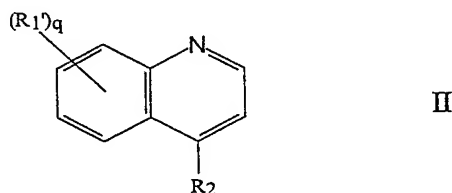
wherein the two components are either mixed for simultaneous use in one homogeneous formulation, or are separated for subsequent use in any order.

2. A composition according to claim 1, wherein said antiseptic is selected from the group consisting of chlorhexidine, thymol, and esters of p-hydroxybenzoic acid selected from methyl, ethyl, propyl, and butyl.
3. A composition according to claim 1, further comprising a component selected from solvents, buffers, carriers, binding agents, stabilizers, adjuvants, diluents, excipients, surfactants, flavors, and odorants.
4. A composition according to claim 1, further comprising another pharmaceutically active substance selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic compounds.
5. A composition according to claim 1, wherein the two components of said two-component composition are applied subsequently, in any order.

6. A composition according to claim 1, wherein the two components of said two-component composition are applied simultaneously.
7. A composition according to claim 1, for topical use.
8. A composition according to claim 7, wherein said use comprises rinsing with liquid, or applying cream, ointment, gel, patch, or spray.
9. A composition according to any one of claims 1 to 8, wherein said stomatitis or mucositis comprises canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous erosive or ulcerative lesions, pemphigus family disorders, pemphigoid family disorders, linear IgA disorders or other immunoregulatory disorders, herpetiform dermatitis, discoid lupus erythematosus, radiotherapeutic mucositis, or chemotherapeutic mucositis.
10. A composition according to claim 9, wherein said mucositis or stomatitis is accompanied by a secondary infection.
11. A composition according to any one of claims 1 to 10, wherein in said quinoline derivative of formula I, as defined in claim 1,

R_1 and R_1' are independently selected from $-Cl$, $-OCH_3$, and $-CF_3$; one of R_2 and R_2' is $-H$, and one of R_2 and R_2' is selected from $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3 - C_5 alkyl, substituted with 1 to 2 substituents selected from C_1 - C_2 alkyl, ethenyl, and $-NH_2$, and wherein either said $-NH_2$ is optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3 - C_5 alkyl or C_1 - C_2 alkyl, possibly forming bicyclic structure; and the sum of p and q is an integer from 1 to 3.

12. A composition according to any one of claims 1 to 11, wherein said quinoline derivative has formula II:



wherein

R_1' is selected from $-Cl$, C_1 - C_3 alkyloxy, and $-CF_3$;

R_2 is selected from $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is C_3 - C_6 alkyl substituted with 1 to 3 substituents selected from C_1 - C_2 alkyl, ethenyl, and $-NH_2$, and wherein said $-NH_2$ is either optionally substituted with one or two groups selected from ethyl

and hydroxyethyl or the nitrogen atom of said -NH_2 is connected with 1 or 2 carbon atoms of said $\text{C}_3\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_2$ alkyl, possibly forming bicyclic structure, and
q is 1 or 2.

13. A composition according to any one of claims 1 to 12, comprising a stereoisomer, or a mixture of stereoisomers, of a quinoline derivative according to claim 1.
14. A composition according to claim 13, wherein the compound of formula I is selected from quinine, quinidine, hydroxychloroquine, and a salt thereof.
15. A composition according to any one of claims 1 to 14, wherein said mucositis comprises canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers, or recurrent aphthous stomatitis.
16. A composition according to claim 15, wherein said mucositis is accompanied by a secondary infection.
17. A method for ameliorating, treating, and preventing an oral mucosa disorder, comprising

- i) providing a quinoline derivative of formula I as defined in claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof;
 - ii) providing an antiseptic;
 - iii) preparing a two-component composition comprising either two formulations containing separately said antiseptic and said quinoline derivative or its isomer or salt, or one formulation comprising a mixture of said antiseptic and quinoline derivative in solution or suspension, wherein said formulations may further comprise components adjusting the consistency, stability, and olfactory properties, and optionally an additional active substances selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic; and
 - iv) administering said formulation or formulations to a patient in need of the treatment, wherein the two components may be administered simultaneously or subsequently.
18. The method of claim 17, wherein said administration of said formulation or formulations comprises rinsing, spraying, and applying ointment or adhesive patch.

19. The method of claim 17, wherein said mucosa disorder is associated with aphtha, and wherein said administration comprises rinsing mouth several times a day.
20. The method of claim 19, wherein said rinsing comprises one liquid containing an antiseptic and a compound of formula I.
21. The method of claim 19, wherein said rinsing comprises two liquids, one comprising an antiseptic, and the other a compound of formula I.
22. The method of claim 21, wherein said antiseptic is chlorhexidine in an alcohol-free water solution.
23. The method of claim 21, wherein said compound of formula I is selected from quinine, quinidine, hydroxychloroquine, and a salt thereof.

לוצאטו את לוצאטו
LUZZATTO & LUZZATTO
By: ע"י: